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(81) Designerade stater AP: all, EP: all, OA: all, AE, AG, AL, AM,
Designated states AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EA, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LI, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

(21) Patentansökningsnummer PCT SE00/00819
Patent application number

(86) Ingivningsdatum 2000-04-28
Date of filing

(30) Prioritet begärd från 1999-04-28 SE 9901531-5
Priority claimed from 1999-05-26 SE 9901906-9
1999-06-15 SE 9902251-9
1999-06-15 SE 9902252-7

Stockholm, 2000-08-11

För Patent- och registreringsverket
For the Patent- and Registration Office

Anita Södervall

Avgift
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PCT REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only	
5000/00819	
International Application No.	
28-04-2000	
International Filing Date	
The Swedish Patent Office PCT International Application	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired)(12 characters maximum)	2001147

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Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Respiratorius AB Sölvegatan 41 SE-223 70 LUND SWEDEN	<input type="checkbox"/> This person is also inventor. Telephone No. Facsimile No. Teleprinter No.
State (that is, country) of nationality: SWEDEN	State (that is, country) of residence: SWEDEN
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Sheet No. 2

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Regional Patent

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| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea +Utility Model | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
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Sheet No. 3

Box No. VI PRIORITY CLAIM		<input checked="" type="checkbox"/> Further priority claims are indicated in the Supplement Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 28 April 1999 (28.04.99)	9901531-5	SWEDEN		
item (2) 26 May 1999 (26.05.99)	9901906-9	SWEDEN		
item (3) 15 June 1999 (15.06.99)	9902251-9	SWEDEN		

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): **1-4**

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

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ISA / SE

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(if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

See continuation
sheet No. 3b enclosed

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 5
description (excluding sequence listing part) : 16
claims : 5
abstract : 1
drawings : 1
sequence listing part of description :

Total number of sheets : 28

Figure of the drawings which should accompany the abstract: 1

This international application is accompanied by the item(s) marked below:


1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference No., if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
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7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
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Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

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28 April 2000



Dan Henriksson

Authorised Agent

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Date of receipt of the record copy by the International Bureau:

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Supplement Box of Box No. VI PRIORITY CLAIM		
Filing date of earlier application (day/month/year)	Number of earlier application	National application: country
Item (4) 15 June 1999 (15.06.99)	9902252-7	SWEDEN
Item (5) 28 April 1999 (28.04.99)	60/131 355	USA
Item (6) 27 May 1999 (27.05.99)	60/136 604	USA
Item (7) 17 June 1999 (17.06.99)	60/139 632	USA
Item (8) 17 June 1999 (17.06.99)	60/139 633	USA

Continuation of Box No. VII INTERNATIONAL SEARCHING AUTHORITY		
Request to use results of earlier search; reference to that search:		
Date (day/month/year)	Number	Country (or regional Office)
11.11.1999 28.04.1999	SE99/00509	SWEDEN
11.11.1999 26.05.1999	SE99/00641	SWEDEN
11.11.1999 15.06.1999	SE99/00813	SWEDEN
11.11.1999 15.06.1999	SE99/00814	SWEDEN

Re. Jcl

MEDICAMENT

Field of the Invention

The present invention relates to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β -aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT₁ type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT₂, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, 334, 1-23 (1997), which is incorporated herein by reference.

Receptors of the 5-HT₂ type are also well known, e.g. through US 5 869 497, US 5 705 519 and US 5 246 935. The relevance of receptors of the 5-HT₂ type has been reported in conjunction with e.g. CNS and neuronal disorders. Such disorders are often treated with compounds having antagonist activity to a receptor of the 5-HT_{2a},

plasma extravasation or mucous secretion caused by e.g. asthma or any other disorder related thereto.

Accordingly, the present invention relates, in one of its aspects, to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

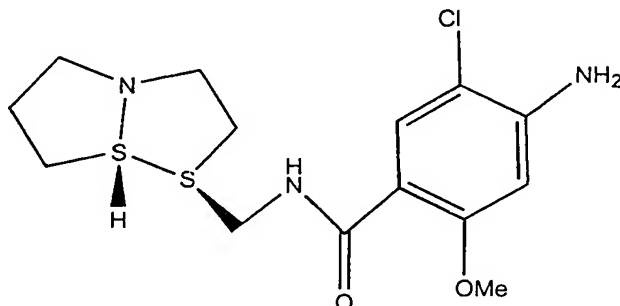
In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

Said bronchocontraction may also occur in conjunction with such disorders as e.g. emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depres-

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The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural

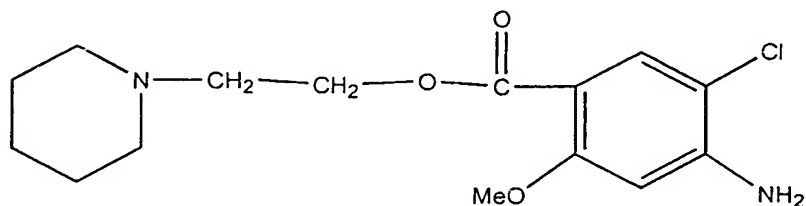
5 formula:



ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidiny)ethylester, having the structural

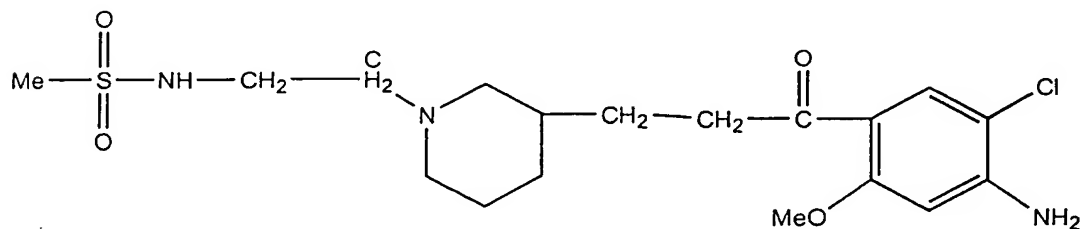
10

formula:



RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidiny]ethyl]-methanesulfonamide monohydrochloride, having the structural

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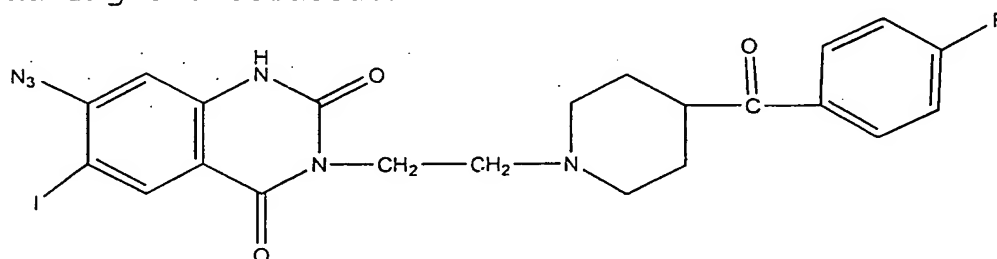


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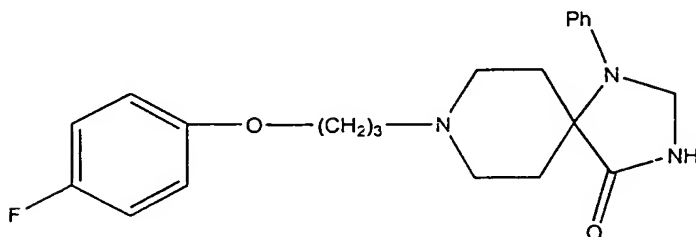
has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT_{2a} receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising ketanserin, AMI-193 or MDL 100 907, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

Thus, the invention also relates to the use of one or more of the above-mentioned compounds, namely: ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-Quinazolin-2-one, having the structural formula:



AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymo-

compound according to the present invention having agonist activity to the 5-HT₄ receptor. Preferably, said method relates to the treatment of asthma and disorders related thereto.

5 The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to the present invention having antagonist activity to a 5-HT_{2a} receptor. Preferably, said
10 method relates to treatment of asthma and disorders related thereto.

Further, the present invention relates to a method for treatment of disorders involving bronchocontraction,
15 wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

The expression "has the capacity of reducing the pathological bronchocontraction by at least ...%" used throughout the present patent application means that the
20 compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT_{2a}-activating properties. The level of contraction in the airways can, for instance, be deter-
25 mined by spirometric measurements of the Forced Expiratory Volume (FEV₁), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV₁ during periods of relatively little obstructive problems.

30 As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT₄
35 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_{2a} receptor is not affected; only the relaxing 5-HT₄ receptor is activated. In the

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preparations. Note that 5-HT only gives a transient relaxation, while selective 5-HT₄ agonists give a strong sustained relaxing effect.

Detailed Description

5 The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in
10 the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

 The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the
15 thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations,
20 the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong,
25 smooth type of tone.

 In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from neuroepithelial endocrine (NEE) cells.

30 Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT₁, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇, as well as on 5-HT₂ receptors.

35 Additional experiments have shown that when 1 μ M serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth

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fect after 5-10 min, which disappears gradually during the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT₄ receptor, and a slower activation of the contracting 5HT_{2a} receptor. This is clear, because activation of the relaxing 5-HT₄ receptor by a substance that lacks 5-HT_{2a} receptor activating properties (such as 5-carboxiamidotryptamine or SC 53116), results in a relaxation that is persistent and not transient (see Fig. 1).

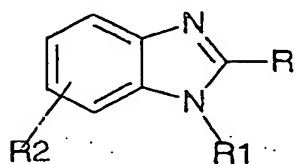
It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT_{2a} activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT₄ receptor results in a relaxing effect, whereas agonist action on 5-HT_{2a} receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT₄ receptor as well as on the contracting 5-HT_{2a} receptor.

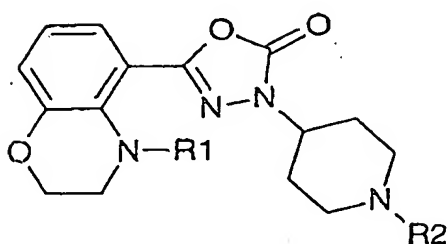
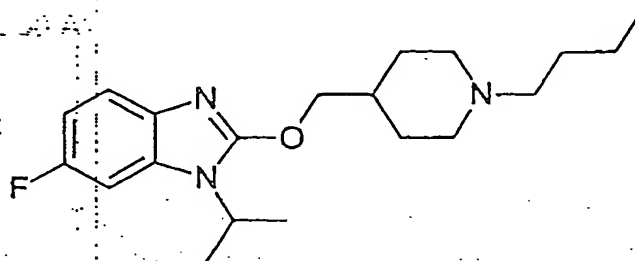
It was also deduced from these experiments that compounds having agonist activity to the 5-HT₄ receptor, while having only low or no agonist activity to a 5-HT_{2a} receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament intended for treatment

Further 5-HT₄ agonist structures useful according to the present invention



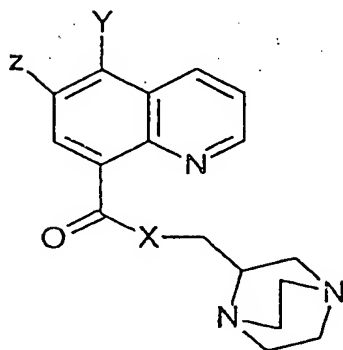
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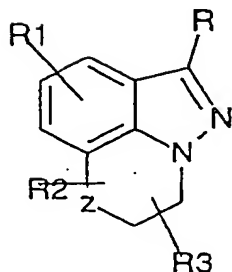
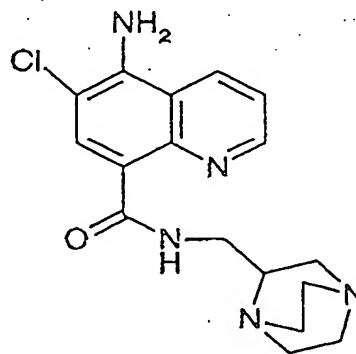
Arylcarbamate derivatives of 1-piperidineethanol
4-amino-5-chloro-2-methoxybenzoic acid esters,
e.g. ML10302, RS 57639 and SR59768

4-amino-5-chloro-2-methoxy-N-((2S,4S)-
1-ethyl-2-hydroxymethyl-4-
pyrrolidiny)benzamide, e.g. TKS159

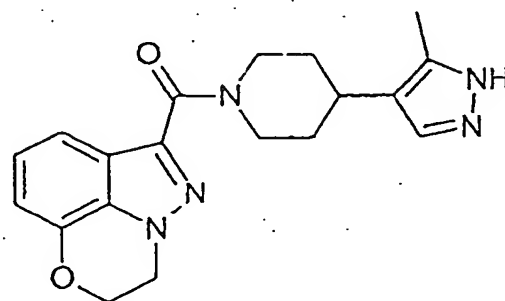
thiophene carboxamide derivatives 3 (a-j)
5. Azabicyclo(x.y.z) derivatives
2-piperazinylbenzoxazole derivatives
2-piperazinylbenzothiazole derivatives, e.g. VB20B7
clebopride
Sandoz compound 1b



particularly



particularly



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CLAIMS

1. Compound having agonist activity to a 5-HT₄ receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT₄ receptor for use as a medicament for treatment of disorders involving bronchocontraction.

2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-carboxamido-tryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimethyltryptamin, ML-1035, ML10302, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389, YM-09151, Zacopride and Zelmac.

3. Compound according to claim 2, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

4. Use of one or more compounds according to claims 1 and 2 having agonist activity to a 5-HT₄ receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT₄ receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

5. Use according to claim 4, wherein said one or more compounds has/have the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and

- 5 wherein said compound(s) is/are chosen from the group comprising 5-carboxamidotryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimethyl-tryptamin, ML-1035, ML10302, 5-metoxytryptamin, Metoclopramide, Mosapride,
- 10 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389,
- 15 YM-09151, Zacopride and Zelmec.

6. Use according to claims 4 and 5, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.
- 20

7. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claim 1.
- 25

8. Compound having antagonist activity to a 5-HT_{2a} receptor; and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_{2a} receptor for use as a medicament for treatment of disorders involving bronchocontraction.
- 30

9. Compound according to claim 8, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising AMI-193 and MDL 100,907,
- 35

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and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimi-
dazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-
(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1
H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramci-
5 clane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymo-
clavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-
methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydro-
chloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY
100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-
10 1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804,
LSD, LU 111995, (S,S) -LY-53,857, (R,S) -LY-53,857,
(S,R) -LY-53,857, (R,R) -LY-53,857, LY-53,857 free base,
LY 215840, MDL-11,939, MDL 28133A, MDL 100,151,
MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-
15 methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one,
methysergide, Mianserin, NE-100, Nefazodone,
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045,
Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine de-
rivatives, Pizotifen, raclopride, Roxindole, Risperidone,
20 Ritanserin, RP62203,
sarpogrelate and its active metabolite (M-1),
serotonin reuptake inhibitors like fluoxetine, YM 992,
medifoxamine, cericlamine, imipramine, iprindole, BIMT
17, citalopram, paroxetine, sertraline, fluvoxamine
25 spiro indoles N-substituted with a 3-(dimethylamino)-
propyl chain
Spiperone, SR 46349B, WAY 100635, WY-50,324,.

10. Compound according to claim 9, wherein said
bronchocontraction appears in asthma and disorders re-
30 lated thereto, emphysema, chronic bronchitis, chronic ob-
structive pulmonary disease, depression, anorectic or bu-
limic eating disorders, anxiety or various psychotic con-
ditions including schizophrenia.

11. Use of one or more of the compounds according to
35 claims 8 and 9 and including ketanserin having antagonist
activity to a 5-HT_{2a} receptor, and derivatives and pharma-
ceutically acceptable salts thereof having antagonist ac-

tivity to the 5-HT_{2a} receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

- 5 12. Use according to claim 11, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising
- 10 ketanserin, AMI-193, MDL 100,907
and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymoclavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY 100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804, LSD, LU 111995, (S,S) -LY-53,857, (R,S) -LY-53,857, (S,R) -LY-53,857, (R,R) -LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine
- 35 spiro indoles N-substituted with a 3-(dimethylamino)-propyl chain
Spiperone, SR 46349B, WAY 100635, WY-50,324,.

13. Use of one or more compounds according to claims 11 and 12 in combination, either simultaneously or sequentially, with a compound having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

14. Use according to claim 13, wherein said compound having agonist activity to the 5-HT₄ receptor is serotonin and derivatives thereof or a compound according to claims 1 and 2.

15. Use according to claims 11-14, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

16. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 11-14.

17. Composition comprising a combination of the compounds defined in claims 13 and 14 for use as a medicament for treatment of disorders involving bronchocontraction.

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ABSTRACT

The present invention relates to a compound having
5 agonist activity to the 5-HT₄ receptor for use as a me-
dicament and to the use of said compounds in the manu-
facture of a medicament for use in therapeutic or prop-
hylactic treatment of disorders involving bronchocontrac-
tion of a human or animal body, as well as methods of
10 treatment, wherein said compounds are administered. The
present invention also relates to a compound having an-
tagonist activity to the 5-HT_{2a} receptor for use as a me-
dicament and to the use of said compound in the manu-
facture of a medicament for use in therapeutic or prop-
15 hylactic treatment of disorders involving bronchocontrac-
tion of a human or animal body, as well as methods of
treatment, wherein said compounds are administered.

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Fig 1

